[ORAL ARGUMENT NOT SCHEDULED]

No. 24-5235

IN THE UNITED STATES COURT OF APPEALS
FOR THE DISTRICT OF COLUMBIA CIRCUIT

NOVARTIS PHARMACEUTICALS CORPORATION,

Plaintiff-Appellant,

v.

DOROTHY FINK, et al.,

Defendants-Appellees,

MSN PHARMACEUTICALS INC., et al.,

Intervenor-Defendants-Appellees.

On Appeal from the United States District Court
for the District of Columbia

BRIEF FOR FEDERAL DEFENDANTS-APPELLEES

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CERTIFICATE AS TO PARTIES, RULINGS, AND RELATED CASES

Pursuant to D.C. Circuit Rule 28(a)(1), the undersigned counsel certifies as follows:

A. Parties and Amici

Plaintiff-Appellant is Novartis Pharmaceuticals Corporation.

Defendants-Appellees are Dorothy Fink, in her official capacity as Acting Secretary of Health and Human Services, and Sara Brenner, in her official capacity as Acting Commissioner of the U.S. Food and Drug Administration (FDA).[1]

Intervenor for Defendants-Appellees are MSN Pharmaceuticals, Inc., and MSN Laboratories Private Limited.

B. Rulings Under Review

Plaintiff-Appellant Novartis appeals from the memorandum and order issued by the Honorable Dabney L. Friedrich (D.D.C. Case No. 1:24-cv-02234) on October 13, 2024, granting defendants-appellees' and intervenor-defendants-appellees' motions for summary judgment and

[1] Pursuant to Federal Rule of Appellate Procedure 43(c)(2), Ms. Fink and Dr. Brenner are automatically substituted for their predecessors.

denying plaintiff-appellant's motion for summary judgment. Dkt. Nos. 64, 65.

C. Related Cases

In a prior appeal in this case, Novartis appealed from the district court's memorandum and order denying Novartis's motion for a preliminary injunction. *Novartis Pharms. Corp. v. Becerra*, No. 24-5186 (D.C. Cir. dismissed Oct. 31, 2024); Dkt. Nos. 22, 23. The Court dismissed that appeal as moot in light of the district court's intervening decision on the merits. Order, *Novartis Pharms. Corp. v. Becerra*, Nos. 24-5186, 24-5235 (D.C. Cir. Oct. 31, 2024).

In January 2025, Novartis filed a new complaint against the government regarding a provision of the law relating to pediatric exclusivity. *Novartis Pharms. Corp. v. Fink*, No. 1:25-cv-00090 (D.D.C. filed Jan. 13, 2025). The district court denied the motion for a temporary restraining order in an oral ruling on January 15, 2025. *See* Minute Order, *Novartis Pharms. Corp.*, No. 1:25-cv-00090 (Jan. 15, 2025).

Novartis and MSN are also engaged in separate proceedings in the Federal Circuit, to which the government is not a party, regarding separate patents that are not at issue here. *See Novartis Pharms. Co. v. MSN Pharms.*,

Inc., Nos. 24-2211, 24-2212 (Fed. Cir. Dec. 4, 2024); *In re Entresto (Sacubitril/Valsartan)*, No. 23-2218 (Fed. Cir. Jan. 10, 2025). Most recently, the Federal Circuit granted Novartis's request for an administrative stay, Corrected Order, *In re Entresto (Sacubitril/Valsartan)*, No. 23-2218 (Jan. 16, 2025), Dkt. 121, and on January 21, 2025, the Federal Circuit granted the motion for reconsideration and enjoined MSN, "until issuance of the mandate in these appeals, from commercial marketing and sale of their generic version of Entresto." Order at 3, *In re Entresto (Sacubitril/Valsartan)*, No. 23-2218 (Jan. 21, 2025), Dkt. 127.

I am not aware of any other related cases.

/s/ Caroline W. Tan
Caroline W. Tan

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GLOSSARY

ACE	Angiotensin-converting Enzyme
ANDA	Abbreviated New Drug Application
ARB	Angiotensin II Receptor Blocker
FDA	U.S. Food and Drug Administration
LVEF	Left Ventricular Ejection Fraction
MSN	MSN Pharmaceuticals Inc. and MSN Laboratories Private Limited

STATEMENT OF JURISDICTION

Plaintiff invoked the district court's jurisdiction under 28 U.S.C. § 1331 in this action under the Administrative Procedure Act. The district court entered summary judgment for defendants on October 13, 2024. Dkt. 68 at 25. Plaintiff timely appealed on October 14, 2024. Dkt. 66. This Court has jurisdiction under 28 U.S.C. § 1291.

STATEMENT OF THE ISSUES

Plaintiff Novartis Pharmaceuticals, Inc., brings this action challenging FDA's approval of a generic version of Entresto, a heart-failure medication owned and marketed by Novartis. The district court rejected each challenge and entered summary judgment for the defendants. The questions presented are:

1. Whether FDA properly applied its own regulations when approving the generic drug's labeling carving out certain patent-protected methods of use from Entresto's labeling.

2. Whether FDA reasonably exercised its scientific judgment in determining that the generic drug's labeling did not render the generic less safe or effective than Entresto for the remaining, nonprotected uses.

3. Whether FDA properly determined that the generic drug and brand-name drug contain the same active ingredients.

PERTINENT STATUTES AND REGULATIONS

Pertinent statutes and regulations are reproduced in the addendum to this brief.

STATEMENT OF THE CASE

A. Statutory and Regulatory Background

Under the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 301 *et seq.*, new drugs may not be sold in the United States without FDA approval. *Id.* § 355(a). To obtain FDA approval, a manufacturer generally must submit a new drug application. *Id.* § 355(b). That application must contain proposed labeling for the drug, along with scientific data and other information showing that the drug is safe and effective if used as instructed on the labeling. *Id.* § 355(b)(1)(A)(i), (vi); *see* 21 C.F.R. § 201.57(c).

To increase competition among drug manufacturers and reduce the expense of approved drugs, the Hatch-Waxman Amendments to the Act provide an abbreviated pathway for premarket approval of generic versions of approved brand-name drugs. Under the amendments, a would-be generic competitor may file an abbreviated new drug application

(ANDA) that "piggy-back[s]" in key respects on an approved new drug application. *Caraco Pharm. Lab'ys, Ltd. v. Novo Nordisk A/S*, 566 U.S. 399, 405 (2012). Instead of providing independent evidence of safety and efficacy, the typical abbreviated new drug application must show, among other things, that the generic drug has the same "active ingredients as . . . the brand-name drug." *Id.*; *see* 21 U.S.C. § 355(j)(2)(A)(ii), (4)(C).

Under FDA regulations, an active ingredient is "identical" to another if it has "the same salt . . . of the same therapeutic moiety." 21 C.F.R. § 314.3(b) (defining "Pharmaceutical equivalents"). The "[a]ctive moiety" is the part of the molecule "responsible for the physiological or pharmacological action of the drug substance." *Id.* Active-ingredient sameness is based on the drugs' chemical identity and not their physical form or shape. *Final Rule: Abbreviated New Drug Application Regulations*, 57 Fed. Reg. 17950, 17958–59 (Apr. 28, 1992); FDA, *Guidance for Industry: ANDAs: Pharmaceutical Solid Polymorphism* 5–6 (July 2007), https://perma.cc/U963-233N.

The Hatch-Waxman Amendments also require that a generic drug include the same labeling as the one approved for the brand-name drug, subject to specified exceptions. *See* 21 U.S.C. § 355(j)(2)(A)(v), (4)(G). One

statutory exception allows differences in labeling for "changes required . . . because the [generic] drug and the [brand-name] drug are produced or distributed by different manufacturers," *id.* § 355(j)(2)(A)(v), an exception that enables generic manufacturers to, among other things, change their labeling to avoid infringing any patents held by the brand-name manufacturer.

"[P]atents [may] come in different varieties. One type protects the drug compound itself. Another kind—the one at issue here—gives the brand manufacturer exclusive rights over a particular *method of using* the drug." *Caraco*, 566 U.S. at 405 (emphasis added). When (as here) the reference drug is covered by unexpired method-of-use patents listed in the FDA's Orange Book—which lists patents relevant to approved drugs—a generic applicant has alternative options to obtain FDA approval to market its generic drug. First, the applicant may certify that it will market its generic drug only after the relevant patents expire. 21 U.S.C. § 355(j)(2)(A)(vii)(III). Second, the applicant may certify its belief that the relevant patents are invalid or would not be infringed by the manufacture or sale of the generic drug. *Id.* § 355(j)(2)(A)(vii)(IV). Such a "paragraph IV certification" is deemed to be an act of patent infringement and may trigger

litigation to determine the validity and scope of the disputed patents. *Caraco*, 566 U.S. at 407; *see* 35 U.S.C. § 271(e)(2)(A). Third, the generic manufacturer may inform FDA that the "method of use patent . . . does not claim a use for which the applicant is seeking approval." 21 U.S.C. § 355(j)(2)(A)(viii).

This case concerns the third option, known colloquially as a "section viii" statement. *Caraco*, 566 U.S. at 406. "A section viii statement is typically used when the . . . brand holds patents on only some approved methods of using the drug." *Id.* A section viii applicant asserts that it "will market the drug for one or more methods of use not covered by the brand's patents." *Id.* In such cases, governing FDA regulations permit a generic labeling that "omi[ts] . . . an indication or other aspect" of the reference drug's labeling that is "protected by patent." 21 C.F.R. § 314.94(a)(8)(iv); *see also id.* §§ 314.94(a)(12)(iii)(A), 314.127(a)(7). A section viii applicant therefore does not violate the Act's same-labeling requirement if it proposes "labeling for the generic drug that 'carves out' from the brand's approved label the still-patented methods of use." *Caraco*, 566 U.S. at 406. But FDA may not approve such an application if the proposed labeling differences "render the proposed drug product less safe or effective than

the listed drug for all remaining, nonprotected conditions of use." 21 C.F.R. § 314.127(a)(7).

"FDA acceptance of the carve-out label allows the generic company to place its drug on the market" immediately, assuming the application meets other requirements, "but only for a subset of approved uses—*i.e.*, those not covered by the brand's patents." *Caraco*, 566 U.S. at 406; *see* 21 C.F.R. § 314.107(b)(1)(ii).

B. Factual Background

1. FDA approves a generic version of Entresto.

Novartis owns and markets Entresto, a widely used heart medication that was first approved by FDA in 2015. Novartis owns four method-of-use patents related to Entresto and relevant here. Three are "use patents" that purportedly[2] cover use of Entresto to treat certain chronic heart failure patients, classified as patients with "preserved" ejection fraction (as distinguished from patients with "reduced" ejection fraction).[3] *See* AR 3930

[2] FDA does not evaluate the patents listed by the brand-name manufacturer, but relies on the use codes submitted by the brand-name manufacturer to describe the patents' purported scope in the Orange Book.

[3] Ejection fraction measures how well the heart is contracting; lower levels indicate lower rates of heart contraction. Am. Heart Ass'n, *Ejection Fraction Heart Failure Measurement*, https://perma.cc/2YJN-R8KQ.

(citing U.S. Patent Nos. 9,517,226; 9,937,143; and 11,135,192). And one is a "dosage patent" that purportedly covers a modified dosing regimen of the drug for a certain subset of patients newer to the medication. *See* AR 3930 (citing U.S. Patent No. 11,058,667).

Entresto's therapeutic effect arises from two substances, sacubitril and valsartan. According to its labeling, Entresto "contains a complex comprised of anionic forms of sacubitril and valsartan, sodium cations, and water molecules in the molar ratio of 1:1:3:2.5, respectively." Dkt. 1-1, at 11 (Entresto Package Insert § 11). "Anionic forms" refers to negatively charged ions of the relevant molecule, and "sodium cations" refers to positively charged sodium ions.

Initially, Entresto was only approved for patients "with chronic heart failure . . . and reduced ejection fraction." AR 19 (2015 Entresto Package Insert § 1.1). That was because Entresto had only been tested among patients with reduced ejection fraction. AR 3923–24 & 3924 n.70 (describing the PARADIGM study); AR 3935. But after Novartis conducted another clinical study (the PARAGON study) involving a broader patient population—this time including patients who had "normal" (not reduced) ejection fraction—FDA approved Entresto's updated labeling that allowed

the drug to be marketed to a broader population. AR 3937–39. Accordingly, Entresto's updated labeling dropped the word "reduced" but added language "suggest[ing] that [Entresto] may not be effective at the upper range of" ejection fraction labels, and that prescribers should "use clinical judgment" when incorporating ejection fraction into their treatment decisions. AR 3940, 4013–14.

In 2019, intervenor-defendants MSN Pharmaceuticals Inc. and MSN Laboratories Private Limited (collectively, MSN) sought FDA approval to market a generic version of Entresto. AR 1688. According to its labeling, MSN's generic drug contains "anionic forms of sacubitril and valsartan, and sodium cations in the molar ratio of 1:1:3, respectively." MSN Package Insert, Dkt. 13-1, at 3 (§ 11). To exclude the uses covered by Novartis's patents, MSN submitted section viii statements with the following two carve-outs:

(1) The Use Carve-Out. The MSN generic's indication carves out from its labeling Entresto's approved use for chronic heart failure patients who could be categorized within prevailing definitions of preserved or normal ejection fraction. The carve-out does so by adding narrowing

language, specifying that MSN's generic is approved only for patients "with chronic heart failure and reduced ejection fraction," as shown below:

Entresto's indication	MSN generic's indication
ENTRESTO is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure. Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal. LVEF is a variable measure, so use clinical judgment in deciding whom to treat. Dkt. 1-1, at 3 (§ 1.1) (alterations added).	Sacubitril and valsartan tablets are indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure~~.~~ **and reduced ejection fraction.** ~~Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal.~~ ~~LVEF~~**Left ventricular ejection fraction (LVEF)** is a variable measure, so use clinical judgment in deciding whom to treat. Dkt. 13-1, at 2 (§ 1.1) (alterations added).

(2) The Dosage Carve-Out. To exclude the use protected by the dosage patent, MSN's labeling omits part of the Entresto labeling that describes a modified dosing regimen for a certain subset of patients who are new to this type of drug. That section, contained in section 2.6 of Entresto's package insert, instructs prescribers to introduce patients with less experience taking "[angiotensin-converting enzyme (ACE)] inhibitor or [angiotensin II receptor blocker (ARB)]" drugs (a different type of drug also

used to treat heart failure) more slowly to Entresto, as consistent with the prescribers' clinical judgment:

> **2.6 Dose Adjustment for Patients Not Taking an ACE inhibitor or ARB or Previously Taking Low Doses of These Agents**
>
> In patients not currently taking an ACE inhibitor or an angiotensin II receptor blocker (ARB) and for patients previously taking low doses of these agents, start ENTRESTO at half the usually recommended starting dose. After initiation, increase the dose every 2 to 4 weeks in adults . . . to follow the recommended dose escalation thereafter.

Dkt. 1-1, at 4 (§ 2.6).

FDA approved this proposed modified dosing regimen after Novartis submitted the results of its "TITRATION" study, which evaluated the safety and tolerability of Entresto. The study compared two groups of patients: a "conservative up-titration" group that initially received a smaller dosage of Entresto ramped up to 200 mg over six weeks, and a "condensed up-titration" group that received an initially larger dosage of Entresto ramped up to 200 mg over three weeks. AR 3925. FDA found that the study showed "Entresto was well tolerated" across both groups, with no meaningful differences in common adverse reactions, including hypotension (low blood pressure), renal dysfunction, and hyperkalemia (excessive potassium). AR 3925; *see* AR 3949. FDA also noted that the

"[a]vailable evidence does not suggest that the safety profile of [Entresto] would be significantly different" for ACE-inhibitor- and ARB-experienced patients as compared to ACE-inhibitor- and ARB-naïve patients. AR 310. FDA nevertheless approved Novartis's modified dosing regimen for ACE-inhibitor- and ARB-naïve patients as "reasonable," noting that gradually increasing the dosage "*may* reduce the risk of hypotension, renal impairment and hyperkalemia" for that subset of patients. AR 3925 (emphasis added) (quotation marks omitted); *see* AR 3925 n.83. FDA stated it was "unknown" whether the modified dosing regimen was the "*safest* and *best-tolerated* option for such patients." AR 3949.

2. Novartis submits citizen petitions to FDA.

Novartis submitted two citizen petitions seeking to limit FDA approval of generics referencing Entresto. One citizen petition (the Active Ingredient petition) asked FDA to refuse approval of any generic that did not contain active ingredients in the exact same physical structure as Entresto, a complex of sacubitril and valsartan derivatives bound together by "ionic interactions." *See* AR 2812, 2814, 2817–31. Novartis argued that FDA regulations required the "active ingredients in the proposed generic drug to have the same physical structure as the active ingredients" in the

reference drug. AR 2813. FDA denied the petition in a 26-page letter, explaining that Novartis's position was inconsistent with FDA's longstanding view that active-ingredient sameness depends on the chemical "identity of [a drug's] individual active ingredients," rather than the physical form or structure (here, a complex, or more specifically, a co-crystal) in which they are arranged. AR 2800–03 & 2803 n.116.

The second citizen petition (the Labeling Petition) asked FDA to refuse approval of any abbreviated new drug application that contained a section viii statement regarding either the use or dosage patents. AR 3962, AR 3974–88. FDA denied that petition in a 45-page letter, explaining why MSN's labeling carve-outs met the governing standards and did not undermine safety or efficacy. AR 3910-54. That same day, in July 2024, FDA approved MSN's application with the two carve-outs described above.

C. Prior Proceedings

Soon after FDA announced its decision, Novartis brought this lawsuit challenging FDA's denial of the two citizen petitions and approval of MSN's generic. Novartis sought emergency relief to block the generic's entry into the market. The district court denied relief on the ground that

Novartis failed to show irreparable harm, but the court committed to resolving the merits of the action within 60 days. Dkt. 23, *Novartis Pharms. Corp. v. Becerra*, No. 24-cv-02234 (D.D.C. Aug. 13, 2024). Novartis appealed from the preliminary-injunction denial and sought an emergency stay pending appeal, which this Court granted. Order, *Novartis Pharms. Corp. v. Becerra*, No. 24-5186 (D.C. Cir. Aug. 19, 2024).

The district court then issued its ruling on the merits, rejecting each of Novartis's challenges to FDA's approval of the generic version of Entresto. Dkt. 68. The court granted summary judgment to the government after determining that approval of MSN's generic is "consistent with FDA regulatory and statutory requirements . . . to have the same label and active ingredients as the reference drug," and that "FDA did not act arbitrarily by excluding part of Entresto's dosing regimen from MSN's generic drug label." Dkt. 68, at 14.

The court first upheld FDA's approval of MSN's use carve-out in the generic drug's indication. Dkt. 68, at 15–18. The court rejected Novartis's argument that D.C. Circuit precedent interpreting the "different manufacturer" exception to permit carve-out labels was no longer good law after *Loper Bright Enterprises v. Raimondo*, 603 U.S. 369, 412 (2024),

explaining that this Court in that case had interpreted the statutory exception on its own rather than defer to the agency. Dkt. 68, at 15 (discussing *Bristol-Myers Squibb Co. v. Shalala*, 91 F.3d 1493 (D.C. Cir. 1996)). The court also rejected the argument that FDA erroneously compared MSN's generic label to a superseded version of the Entresto reference label, explaining that the record "unequivocally shows that FDA compared the generic label to [the] 'most recently approved' Entresto label." Dkt. 68, at 15. The court further determined that FDA approval of MSN's indication for use in reduced ejection fraction patients was not arbitrary and capricious given, among other things, FDA's technical expertise in medical determinations and Novartis's acknowledgement that ejection fraction is a relevant diagnostic criterion. Dkt. 68, at 17–18.

In addition, the court concluded that FDA had properly interpreted its own regulations when it approved a generic labeling that omitted a patent-protected indication by adding words to the reference labeling. Dkt. 68, at 16 (citing 21 C.F.R. § 314.94(a)(8)(iv)). The court rejected Novartis's argument that an "omission" under FDA regulations could only mean deletion of words, reasoning that the regulation "must turn on the 'substance of the information that is omitted—not whether that substantive

omission is accomplished by adding words or deleting them.'" Dkt. 68, at 16. The court held that Novartis's position to the contrary is inconsistent with the plain text of the law, erroneously put "form over substance," and led to illogical results, where a generic drug indication statement that stated a drug's approval to treat "Type I, Type II, and Type III" Disease would permit carve-outs but a more general statement that a drug is approved "to treat all types of Disease" would not. Dkt. 68, at 16 (quotations omitted).[4]

Next, the district court upheld FDA's approval of MSN's dosage carve-out, explaining that the agency had provided a "reasoned scientific basis for its conclusion that carving out section 2.6 will not render MSN's generic drug less 'safe or effective'" for all remaining, nonprotected conditions of use. Dkt. 68, at 19 (quoting 21 C.F.R. § 314.127(a)(7)). As discussed, section 2.6 of Entresto's labeling recommends that certain patients new to this type of drug be introduced to Entresto by slowly up-

[4] The district court also rejected Novartis's argument that a statutory provision governing the omission of pediatric indications "implies that language additions are forbidden in other contexts." Dkt. 68, at 16 n.6 (discussing 21 U.S.C. § 355a(o)). Novartis does not renew this argument on appeal.

titrating the dosage according to a specific dosing regimen. In upholding FDA's decision-making here as reasonable, the court emphasized that even though FDA approved the modified regimen, the agency never stated that the modification is the "safest and best-tolerated option for relevant patients." Dkt. 68, at 20 (quotations omitted). Indeed, the court noted, FDA had identified limitations in the Novartis study that formed the basis for the modified dosing regimen. Dkt. 68, at 20.

The court also accepted FDA's determination that the risk of adverse reactions under the remaining, nonprotected conditions of use "can be adequately managed" through other parts of Entresto's labeling describing dose management strategies, *see* Dkt. 1-1, at 6 (Entresto packaging insert §§ 5.3–5.5); Dkt. 13-1, at 2 (MSN packaging insert §§ 5.3–5.5), particularly when considered in the context of longstanding medical guidance recommending a gradual dosage approach in this type of treatment. Dkt. 68, at 20–21 (quotations omitted). The court explained: "In making this safety and efficacy determination, FDA evaluated the clinical significance of the TITRATION study, prevailing medical guidance, and prescriber best practices. It provided a reasoned basis for its decision and concluded, in three separate instances in its thorough citizen petition response, that

carving out Section 2.6 would not render the drug any less 'safe or effective,' *see* 21 C.F.R. § 314.127(a)(7). It cannot be said that the agency applied the wrong standard, inadequately explained its decision, or rendered a clear error of judgment." Dkt. 68, at 21 (citations and quotations omitted).

Finally, the court upheld FDA's determination that MSN's generic met the governing law regarding active-ingredient sameness. Dkt. 68, at 21–24 (first citing 21 C.F.R. § 314.92(a)(1); and then citing 21 U.S.C. § 355(j)(2)(A)(ii)). The court found FDA's determination of active-ingredient sameness to be "rational, carefully explained, and consistent with the record evidence." Dkt. 68, at 24. The court "defer[red] to FDA's factual determination that Entresto and MSN's generic contain the same two active ingredients—sacubitril sodium and valsartan disodium," and it explained that FDA's determination that "Entresto and MSN's generic contain the same compounds with the same chemical identities" is a "pure scientific judgment" that deserves a "high level of deference" and that a court is ill-equipped to second-guess. Dkt. 68, at 22, 24 (quotations omitted).

The court further rejected Novartis's efforts to identify a distinction between the two drugs, explaining that Entresto's purportedly different physical structure as a co-crystal "is irrelevant to the sameness inquiry" under longstanding FDA precedent stating that active-ingredient sameness turns on chemical identity and not physical form. Dkt. 68, at 23, 24. The court also dismissed Novartis's argument that FDA's use of a more specific scientific term to describe Entresto's active ingredients represented a change in agency position, explaining that the more specific term was already consistent with Entresto's own labeling and so did not establish any difference in chemical identity. Dkt. 68, at 23.

After the district court issued its summary-judgment decision and entered final judgment, Novartis filed a separate appeal from that order (the one under review here). At FDA's and MSN's request, this Court dismissed the preliminary-injunction appeal as moot and lifted the prior stay pending appeal of that earlier decision. Order, *Novartis*, No. 24-5186 (Oct. 31, 2024).

More than two months later, Novartis sought an emergency stay pending appeal of the summary-judgment order. *See* Emergency Mot., Jan. 12, 2025. This Court denied the stay on the ground that Novartis "ha[d]

not shown a likelihood of success on its arguments that the FDA's approval of MSN's abbreviated new drug application is in excess of its statutory jurisdiction, or is arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law on the record before us." Order 1, Jan. 16, 2025 (first citing 5 U.S.C. § 706(2)(A), (C); then citing *Rempfer v. Sharfstein*, 583 F.3d 860, 867 (D.C. Cir. 2009); then citing *Bristol-Myers Squibb Co.*, 91 F.3d at 1499–1500; and then citing 21 U.S.C. § 355(j)(2)(A)(v)). This Court also explained that Novartis had failed to request a stay from the district court or explain why doing so would have been impracticable. *Id.* at 1–2.

In January 2025, Novartis filed a new complaint against the government, arguing that FDA should be ordered to convert the approval of MSN's abbreviated new drug application into a tentative approval—thus prohibiting MSN from marketing its drug—based on a provision of the Federal Food, Drug, and Cosmetic Act relating to pediatric exclusivity, 21 U.S.C. § 355a(c)(1)(B)(ii). *See Novartis Pharms. Corp. v. Fink*, No. 1:25-cv-00090 (D.D.C. filed Jan. 13, 2025). According to Novartis, the period of pediatric exclusivity would last until July 15, 2025. The district court denied Novartis's motion for a temporary restraining order in an oral ruling on January 15, 2025. *See* Minute Order, *Novartis Pharm. Corp.*, No.

1:25-cv-00090 (Jan. 15, 2025). The court has not yet ruled on the preliminary-injunction motion. *Id.*

Novartis and MSN are also engaged in separate proceedings in the Federal Circuit, to which the government is not a party, regarding separate patents that are not at issue here. *See Novartis Pharms. Co. v. MSN Pharms., Inc.*, Nos. 24-2211, 24-2212 (Fed. Cir. Dec. 4, 2024); *In re Entresto (Sacubitril/Valsartan)*, No. 23-2218 (Fed. Cir. Jan. 10, 2025). The Federal Circuit had temporarily enjoined MSN from marketing its generic, but as of December 5, 2024, the court had lifted all stays or injunctions against market entry of the generic except for one order that pertained to a patent due to expire on January 15, 2025. *See* Order, *Novartis Pharms. Corp.*, Nos. 24-2211, 24-2212 (Dec. 5, 2024), Dkt. 81. On January 10, 2025, that one remaining stay was lifted. Order, *In re Entresto (Sacubitril/Valsartan)*, No. 23-2218 (Jan. 10, 2025), Dkt. 109. On January 15, 2025, Novartis sought emergency reconsideration and both panel and en banc rehearing. Emergency Mot., *In re Entresto (Sacubitril/Valsartan*), No. 23-2218 (Jan. 15, 2025), Dkt. No. 115. The Federal Circuit granted an administrative stay on January 16, 2025, Corrected Order, *In re Entresto (Sacubitril/Valsartan)*, No. 23-2218 (Jan. 16, 2025), Dkt. No. 121, and on January 21, 2025, the Federal

Circuit granted the motion for reconsideration and enjoined MSN, "until issuance of the mandate in these appeals, from commercial marketing and sale of their generic version of Entresto." Order at 3, *In re Entresto (Sacubitril/Valsartan)*, No. 23-2218 (Jan. 21, 2025), Dkt. No. 127.

SUMMARY OF ARGUMENT

Congress passed the Hatch-Waxman Amendments to increase competition among pharmaceutical companies and lower the cost of prescription drugs. To do so, it created an abbreviated pathway for the market entry of generic drugs that contain, among other things, the same active ingredients and same labeling as the reference drug, subject to specified exceptions. One common application of those exceptions is approval of a generic's labeling that carves out the patent-protected methods of use from the reference drug labeling. Consistent with this well-established process, FDA approved a generic version of Entresto, manufactured by MSN, to enter the market. Novartis challenges that approval based not on any purported patent infringement, but instead on the way that the generic drug's labeling carved out patent-protected methods of use, as well as FDA's determination that the generic and brand-

name drugs contain the same active ingredients. The district court correctly rejected each argument.

1. The Hatch-Waxman scheme specifically allows differences in labeling when the generic drug and the reference drug have different manufacturers. 21 U.S.C. § 355(j)(2)(A)(v). FDA, this Court, and the Supreme Court have consistently understood that provision to allow generic manufacturers to carve out patent-protected uses from their labeling, and indeed, several other provisions of the Hatch-Waxman Amendments make clear that Congress intended them to be able to do so. *See* 21 C.F.R. § 314.94(a)(8)(iv); *Bristol-Myers Squibb Co. v. Shalala*, 91 F.3d 1493, 1499–1500 (D.C. Cir. 1996); *Caraco Pharm. Lab'ys, Ltd. v. Novo Nordisk, A/S*, 566 U.S. 399, 406 (2012); 21 U.S.C. § 355(j)(2)(A)(viii).

As discussed below, FDA approved a generic labeling that properly carved out methods of use purportedly protected by Novartis's patents. Entresto is approved for use in patients with chronic heart failure: those described by Novartis as having "preserved" ejection fraction (a use purportedly covered by Novartis's patent), and those described as having "reduced" ejection fraction. MSN's labeling omits the use covering "preserved" ejection-fraction patients by describing the drug as indicated

for patients with "chronic heart failure and reduced ejection fraction." Dkt. 13-1, at 2 (§ 1.1). The district court correctly upheld FDA's approval of this carve-out.

Novartis's counterarguments misunderstand the law and record. Contrary to its argument (at 42–43), the Supreme Court's decision in *Loper Bright Enterprises v. Raimondo*, 603 U.S. 369 (2024), does not invalidate this Court's binding precedent allowing the use of carve-out labeling. *See Bristol-Myers Squibb Co.*, 91 F.3d at 1499–1500. *Loper Bright* expressly did not "call into question prior cases that relied on the *Chevron* framework," 603 U.S. at 412, and in any event, this Court did not rely on deference to FDA in interpreting the statutory exception. Novartis is also wrong to argue that FDA impermissibly reverted to a previous version of Entresto's labeling—a premise that the district court explained was "unequivocally" contradicted by the record. Dkt. 68, at 15 (citing AR 2402–03).

FDA also did not misunderstand its own regulations regarding the appropriate way to "omit" a patent-protected indication. As the regulations themselves contemplate, and as the district court explained, what is relevant is the "omission of an indication or other aspect of labeling" and not the omission of particular words on the reference

labeling. 21 C.F.R. § 314.94(a)(8)(iv). Novartis's other arguments about the relevance and clinical value of "ejection fraction" as a diagnostic tool are also unsupported and contradicted by its contentions in other parts of its briefing and by Entresto's own labeling.

2. The district court was also correct to uphold FDA's application of its own regulations regarding safety and efficacy. 21 C.F.R. § 314.127(a)(7). As explained, FDA approved a carve-out that omitted a purportedly patented dosing regimen for a subset of patients from MSN's labeling. As described by Novartis, that regimen recommends introducing certain patients to Entresto more slowly according to the regimen's particular schedule.

As both FDA and the district court have explained, Novartis's contrary position is based on the mistaken premise that the modified dosing regimen is the best approach for the relevant subset of patients, as opposed to merely being a regimen included in the brand labeling (the omission of which does not itself render a generic drug less safe). The record shows that FDA approved the inclusion of Novartis's modified dosing regimen as a "reasonable" way to manage certain risks, AR 301, but it never determined that the underlying study supporting the regimen

showed that the modified approach was the "*safest* and *best-tolerated* option for such patients," AR 3949. As FDA explained, there were a number of limitations involved in the underlying study, which in any event did not support the conclusion that there were meaningful safety differences between patients taking a modified dose versus a standard dose of Entresto. AR 3949–50. Accordingly, FDA has never concluded that the modified regimen was necessary such that any deviation raised safety or efficacy concerns. FDA instead concluded that the modified dosing regimen was not unsafe, such that Novartis could choose to include the regimen on the drug's labeling.

FDA also reasonably concluded that other aspects of the MSN generic's labeling, considered in the context of longstanding medical guidance regarding heart-failure treatment, would adequately ensure that the general concerns addressed by the modified dosing regimen would be considered when providers prescribe the generic version of the drug. Those other aspects of the labeling identify the very same risks covered by the modified dosing regimen and expressly acknowledge dose reduction as a mitigation strategy. And it is undisputed that well-established medical guidance recommends a gradual dosage approach for heart-failure

patients. The district court credited this conclusion as reasonable and well-supported, Dkt. 68, at 21, and Novartis provides no basis to question that determination on appeal.

3. The district court also properly upheld FDA's determination that both Entresto and the generic drug have the same active ingredients, meaning they are composed of the "same salt" of the "same therapeutic moiety." 21 C.F.R. § 314.3(b). That much is clear from the face of both drugs' labeling, which contain identical language explaining that the active ingredients are the "anionic forms of sacubitril and valsartan, and sodium cations in the molar ratio of 1:1:3." Dkt. 13-1, at 3 (§ 11) (labeling for MSN generic); *see* Dkt. 1-1, at 11 (§ 11) (same for Entresto, and also listing water molecules).

Faced with the identical language of the labeling, Novartis attempts to engineer a distinction based on one page of the record, but its arguments there amount to a nomenclature distinction and not any difference in chemical identity. Novartis argues that the generic drug is composed of "sacubitril sodium and valsartan disodium," whereas Entresto (per its labeling) is composed of the "anionic forms of sacubitril and valsartan" and "sodium cations." Br. 54 (quotations omitted). But those are the same

thing, as the district court recognized. And FDA's scientific determination about molecular structure is, in any event, precisely the type of "scientific judgment within [FDA's] 'area of expertise'" that is entitled to a "high level of deference" from this Court. *Rempfer v. Sharfstein*, 583 F.3d 860, 867 (D.C. Cir. 2009) (quotations omitted).

STANDARD OF REVIEW

Grants of summary judgment are reviewed de novo. *Ipsen Biopharmaceuticals, Inc. v. Becerra*, 108 F.4th 836, 840 n.1 (D.C. Cir. 2024). Like the district court, this Court reviews an agency's action to determine whether it was "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A). "The scope of review under the 'arbitrary and capricious' standard is narrow and a court is not to substitute its judgment for that of the agency." *Motor Vehicle Mfrs. Ass'n of the U.S. v. State Farm Mut. Auto. Ins. Co.* (*State Farm*), 463 U.S. 29, 43 (1983). Instead, a court considers only whether the agency "examine[d] the relevant data and articulate[d] a satisfactory explanation for its action[s]" and whether, in reviewing the explanation, the agency's "decision was based on a consideration of the relevant factors and whether there has been a clear error of judgment." *Id.* (quotations omitted).

ARGUMENT

FDA properly applied the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act by approving MSN's generic version of a popular heart medication and giving consumers more affordable access to life-saving drugs. The district court properly rejected each of Novartis's challenges.

I. FDA Properly Approved MSN's Use Carve-out.

The Federal Food, Drug, and Cosmetic Act permits a generic drug's labeling to differ from the reference drug's labeling for "changes required . . . because the [generic] drug and the [reference] drug are produced or distributed by different manufacturers." 21 U.S.C. § 355(j)(2)(A)(v). Pursuant to FDA regulations implementing this provision, the agency can approve abbreviated new drug applications if the generic drug's labeling differs through "omission of an indication or other aspect of labeling protected by patent." 21 C.F.R. § 314.94(a)(8)(iv). Relevant here, if an abbreviated new drug application proposes labeling that carves out a patent-protected use of the brand-name drug, then FDA can lawfully approve the application prior to patent expiry, and the generic

drug may enter the market for uses not covered by the brand-name drug's patent.

FDA's approval of MSN's application here easily meets the above standard. Entresto is approved for use in two presentations of patients with chronic heart failure: those who could be categorized within prevailing definitions as having "preserved" ejection fraction and those categorized as having "reduced" ejection fraction. Only the former use is covered by Novartis's description of its method-of-use patent. MSN's labeling omits this use by describing the drug as indicated for "adult patients with chronic heart failure and reduced ejection fraction." Dkt. 13-1, at 2 (§ 1.1).

1. As explained above, the Hatch-Waxman Amendments provide an exception to the same-labeling requirement for "changes required . . . because the [generic] drug and the [reference] drug are produced or distributed by different manufacturers." 21 U.S.C. § 355(j)(2)(A)(v). This Court has long interpreted the "different manufacturer" exception to permit FDA approval of an abbreviated new drug application "even though the label of the generic product will not include one or more indications that appear on the label of the [reference]

drug upon which the [application] is based." *Bristol-Myers Squibb Co. v. Shalala*, 91 F.3d 1493, 1499–1500 (D.C. Cir. 1996) (quotations omitted). Novartis argues, however, that the statutory exception permits *only* "differences in generic labeling to identify a different manufacturer, product name, or company address." Br. 42. But such an interpretation would bar FDA from carving out any uses at all—an argument this Court rejected in *Bristol-Myers Squibb* based on a thorough review of the statute's text, structure, and legislative history. Such an interpretation is also incompatible with the Supreme Court's extensive discussion of carve-out labels in *Caraco Pharmaceutical Laboratories, Ltd. v. Novo Nordisk A/S*, 566 U.S. 399, 406 (2012). Such labels are authorized by a specific statutory provision, 21 U.S.C. § 355(j)(2)(A)(viii), which would make no sense if Novartis's interpretation of the statute were adopted.

To get around this, Novartis suggests that *Bristol-Myers Squibb* is no longer good law after *Loper Bright Enterprises v. Raimondo*, 603 U.S. 369 (2024). Br. 42–43. But *Loper Bright* explicitly did "not call into question prior cases that relied on the *Chevron* framework," and the Supreme Court emphasized that pre-*Loper Bright* decisions upholding specific agency actions are still "subject to statutory *stare decisis* despite [the] change in

interpretive methodology." 603 U.S. at 412. And, in any event, this Court in *Bristol-Myers Squibb* did not rely on deference to FDA in interpreting the different-manufacturers exception. *See* 21 U.S.C. § 355(j)(2)(A)(v). Instead, the Court agreed with the Secretary's interpretation of the statute after its own examination of the statute's text, structure, and legislative history, reasoning, among other things, that such an interpretation best harmonized various provisions of the statute. 91 F.3d at 1499–1500. That legal analysis remains binding on this Court.

2. Novartis is similarly mistaken to contend that FDA has impermissibly reverted to a previous version of Entresto's labeling. Br. 43–44. As the district court explained, the record "unequivocally shows" the opposite: that FDA compared the generic label to the "most recently approved" Entresto label from April 2024. Dkt. 68, at 15; *see* AR 2397, 2402–03 (FDA "labeling review" comparing the generic to the "most recently approved" new drug application for Entresto, dated "04/12/2024" (capitalization altered)).

Novartis complains that the approved MSN labeling matches a prior version of Entresto's labeling. But it is unsurprising that carving out the purportedly patented use from the current Entresto labeling would yield a

labeling similar to the one in use before the purportedly patented use was approved and added to the labeling. As explained above (*see supra* pp. 7–8), Entresto had previously been indicated for patients with "chronic heart failure . . . and reduced ejection fraction"—language that matches MSN's approved indication—because Novartis's prior clinical study had only tested patients in that population. AR 19. After Novartis submitted results from another clinical study that tested a broader subset of patients (including those who could be categorized within prevailing definitions of preserved or normal ejection fraction), FDA approved the broader labeling used today. That the prior version of Entresto's labeling is the same as MSN's approved indication is not evidence that FDA improperly "resurrect[ed]" Entresto's old indication, Br. 44, but rather demonstrates that FDA approved the portion of the indication that was not covered by Novartis's listed description for the use patents. As the district court explained, "[s]imply because the language of the generic label tracks Entresto's original superseded label, it does not follow that [] FDA 'reverted back' to Entresto's original label"—and, again, the record shows the exact opposite. Dkt. 68, at 15; *see* Dkt. 13–1, at 2 (§ 2.2).

3. Novartis fares no better in suggesting that FDA misunderstood its own regulations, which permit a generic labeling's "omission" of a patent-protected indication or other aspect of labeling. 21 C.F.R. § 314.94(a)(8)(iv). Novartis contends that MSN's labeling is defective because it "add[s] to Entresto's labeling" when "omit" means to "leave something out." Br. 45, 47–48. Novartis misunderstands the governing regulation, which contemplates "omission of an indication or other aspect of labeling"—what FDA approved here—and not omission of particular words on the reference labeling. 21 C.F.R. § 314.94(a)(8)(iv). As discussed, Entresto is approved for patients with "chronic heart failure," Dkt. 1-1, at 3 (§ 1.1), and MSN is approved for a narrower subset of those patients: those with chronic heart failure and reduced ejection fraction, Dkt. 13-1, at 2 (§ 1.1). MSN's indication thus excludes—or leaves out, to put it in Novartis's terms—from Entresto's labeling those chronic heart failure patients who could be categorized within prevailing definitions of preserved or normal ejection fraction. FDA's approval here is thus completely consistent with the terms of the governing regulations.

Under Novartis's understanding, however, a generic manufacturer may "omit" a patent-protected use only by deleting words rather than by

adding them, irrespective of the limiting effect that additional words may have on the label's meaning. *See* Br. 44–48. The district court correctly rejected this argument, which would turn agency approval into a word game elevating stylistic decisions over the substance of the labeling. Dkt. 68, at 16. As the district court explained: "Under Novartis's position, a generic drug indication statement that a '[patented drug] is approved to treat Disease (Type I, Type II, and Type III)' would permit carveouts, whereas a statement that a '[patented drug] is approved to treat all types of Disease' would not." Dkt. 68 at 16 (alterations in original). Nothing in the governing regulations suggests that a concise indication statement, such as the one approved for Entresto, precludes carve-out labeling, while a longer statement that happens to separately list each approved use (and conveys the same meaning) would permit it. *See* AR 3946. In addition to elevating form over substance, that outcome is at odds with one of the fundamental purposes of the Hatch-Waxman Amendments to speed generic competition.

For similar reasons, this Court should reject Novartis's argument that FDA is permitted only to omit an entire indication, rather than "redline" a portion of an indication. Br. 43. Once again, it should not matter whether

related uses are grouped together as part of a single indication or listed separately. The statute contains no such distinction, and the regulation sweeps broadly by contemplating omission of "an indication or other aspect of labeling protected by patent." 21 C.F.R. § 314.94(a)(8)(iv).

4. Novartis is also plainly wrong to suggest that the generic's labeling adds a new condition of use "not previously approved for Entresto"—in this case, the statement that ejection fraction "is a variable measure," so prescribers should "use clinical judgment in deciding whom to treat." Br. 46–47. Novartis makes no effort to show how this general statement is a "condition of use," as opposed to clarifying language that contextualizes the extent to which prescribers should rely on ejection fraction measures. *See* AR4013-14. But more fundamentally, there is no dispute that this statement is included verbatim in both Entresto's and MSN's generic labeling (section 1.1 in both)—invalidating any argument that the MSN labeling somehow creates a "new" condition of use. Br. 46. Novartis's effort to get around this hurdle by comparing MSN's labeling to the now-superseded indication for Entresto is beside the point and contradicts its position in other parts of its brief, *see* Br. 41–44 (arguing

without support that FDA unlawfully compared MSN's generic labeling to the superseded version of Entresto's).

5. Novartis further contends that FDA's approval of the generic's labeling is arbitrary and capricious because Entresto's approved indication is qualitative, but the generic's labeling indication for patients with "reduced ejection fraction" imports a quantitative measurement such that there has been an unexplained change in agency position. *See* Br. 48–51. Again, the district court correctly rejected this argument, Dkt. 68, at 17–18, which first rests on the mistaken assumption that MSN's generic labeling adopts a "strictly quantitative" approach at all. Br. 49. MSN's labeling does not include a numeric cutoff, and though the labeling includes the term "reduced ejection fraction," FDA has never defined that metric with respect to any numeric cutoff. *See generally* AR 3920–21, 3935–37. In addition, MSN's labeling—like Entresto's—also recognizes that ejection fraction is a "variable measure" so prescribers should use their "clinical judgment." Dkt. 13-1, at 2 (§ 1.1) (MSN); Dkt. 1-1, at 3 (§ 1.1) (Entresto); *see* Br. 48 (arguing that this precaution emphasizes the qualitative approach in Entresto's labeling). Whether it would be arbitrary and capricious to

approve an indication according to a numerical cutoff is irrelevant because FDA did no such thing.

Novartis's suggestion that use of ejection fraction is somehow out of step with scientific thinking is also undermined by Entresto's own labeling, which acknowledges the medical relevance of ejection fraction as a diagnostic criterion. *See* Dkt. 68, at 18; *see* Dkt. 1-1, at 3 (§ 1.1) (Entresto labeling) ("Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal. LVEF is a variable measure, so use clinical judgment in deciding whom to treat . . . ."). To the extent that Novartis means to suggest that ejection fraction is not sufficiently well defined to make the generic labeling meaningful, that essentially amounts to a critique of Novartis's own patents that purportedly claim the use of the drug in patients with preserved ejection fraction. And in any event, as the district court observed, the medical relevance of a diagnostic tool falls within FDA's scientific and technical expertise. Dkt. 68, at 17; *see Rempfer v. Sharfstein*, 583 F.3d 860, 867 (D.C. Cir. 2009) (this Court owes a "high level of deference" to "scientific judgment[s] within [FDA's] 'area of expertise'" (quotations omitted)).

Finally, Novartis's arguments that FDA's action was arbitrary and capricious are belied by the administrative record, which thoroughly explains the rationale for Novartis's current indication statement. *See* AR 3946; AR 4013 ("The updated labeling statement includes patients who would be within these prevailing definitions of [heart failure with reduced ejection fraction] or [heart failure with preserved ejection fraction]—with information in Section 14 [describing clinical studies] that provides greater clarity on which patients see the most benefit than did Novartis's proposed terms.").

II. MSN's Dosage Carve-Out Does Not Render the Generic Drug Less Safe or Effective for the Remaining Nonprotected Conditions of Use.

FDA properly concluded that the omission of a patented dosing regimen from MSN's labeling did not "render the proposed drug product less safe or effective than the listed drug for all remaining, nonprotected conditions of use." 21 C.F.R. § 314.127(a)(7). Novartis's contrary position is based on the premise that its dosing regimen (found in section 2.6 of Entresto's labeling) is the *best* approach for patients who are new to or less experienced with this type of drug. That premise is wrong. As explained below, FDA approved the section 2.6 regimen as a "reasonable" way to

manage certain adverse risks. AR 301. FDA never determined that the omission of the modified regimen rendered the drug less safe and effective for those patients, as Novartis now contends. *See* Br. 29–31, 38. Novartis's challenge here thus rests on a fundamental misunderstanding of FDA's actions and should be rejected.

1. FDA approved the modified dosing regimen in section 2.6 based on the results of a study called "TITRATION." Again, that study did not establish that the standard dosing regimen put certain patients at a greater risk of adverse reactions. To the contrary, FDA explained that it was "unknown" whether the study showed that the modified dosing regimen was the "*safest* and *best-tolerated* option" for patients new to this type of drug, because "initiation using this dosing regimen has only been studied in an uncontrolled manner." AR 3949. Among other limitations, FDA explained that the study's patients had already demonstrated a certain level of tolerance to Entresto, "limiting generalizability to truly naïve patients," and that the study was not primarily aimed at comparing the effects of dose adjustment. AR 3949.

Moreover, as FDA explained in its letter, the TITRATION study actually showed similar safety profiles between patients taking the

modified dose versus the standard dose of Entresto. AR 3949–50. As FDA observed, the "rates of hypotension, renal dysfunction, and hyperkalemia observed in TITRATION were similar between" the modified- and standard-dose patients. AR 3949. And while the study suggested that patients new to this type of drug "*might* benefit from a slow up-titration regimen," the results "are not robust" and "do[] not provide a scientific basis to conclude, as [Novartis] assert[s] in [its] Petition, that the standard Entresto dosing regimen puts such patients at a greater risk of adverse reactions or that section 2.6 is 'critical' to ensuring the safe and effective use of a generic sacubitril and valsartan product." AR 3949–50.

In short, FDA has never concluded that Entresto would be less safe or effective if its labeling did not identify the modified dosing regimen. Instead, the agency concluded that Novartis could—though was not necessarily required to—include the modified dosing regimen on the drug's labeling. Novartis thus misunderstands the significance of FDA's statement that it "agree[d] with the proposed titration strategy from a safety perspective." AR 311; *see* Br. 29, 38. As discussed, all that statement says is that FDA determined that including the regimen was reasonable—

not that the regimen was so important that any deviation from the regimen raised safety or efficacy concerns.

2. Putting aside the specifics of the regimen, FDA also determined that MSN's generic drug with the regimen carved out is no less safe or effective than Entresto for the remaining nonprotected conditions of use because other aspects of the MSN generic's labeling, evaluated in the context of longstanding medical guidance, ensure that relevant safety concerns are considered when the generic version of the drug is prescribed. That determination was reasonable and properly credited by the district court. Dkt. 68, at 18–21; *see State Farm*, 463 U.S. 29, 43 (1983) (a court must ask only whether the agency "examine[d] the relevant data and articulate[d] a satisfactory explanation for its action[s]"); *Fox v. Clinton*, 684 F.3d 67, 75 (D.C. Cir. 2012) (a court's review of "matters relating to an agency's areas of technical expertise" is "fundamentally deferential" (alteration and quotations omitted)).

Sections 5.3 through 5.5, under the heading "Warnings and Precautions," independently alert providers to the very same risks covered by the omitted section 2.6 labeling—hypotension, impaired renal function, and hyperkalemia—and make clear that dose reduction may be warranted

to mitigate each of those risks. *See* Dkt. 13-1, at 2 (§§ 5.3–5.5) (capitalization altered); AR 243; AR 3950. Moreover, there is no dispute that well-established medical guidance recommends introducing heart-failure patients more slowly to new drugs as "guided by [the patient's] tolerability." AR 3950. FDA thus reasonably determined that health-care practitioners had adequate information, without the section 2.6 dosing regimen, "to determine an appropriate initial dose" of the drug for the nonprotected conditions of use that remain in the generic labeling. AR 3950. As the district court explained, FDA reached its safety-and-efficacy determination based on its own assessment of the "clinical significance of the TITRATION study, prevailing medical guidance, and prescriber best practices." Dkt. 68, at 21. That is precisely the type of "scientific judgment within [FDA's] 'area of expertise'" that is entitled to a "high level of deference" from this Court. *Rempfer*, 583 F.3d at 867 (quotations omitted).

Novartis's contrary arguments here miss the point. *See* Br. 31–33. Novartis is correct that these sections do not state or imply that a provider should use a particular dosing regimen—rendering immaterial its argument, made for the first time on appeal (at 33), that FDA violated the prohibition on implying or suggesting dosing regimens in sections of the

labeling other than the dosage section, *see* 21 C.F.R. § 201.57(c)(3)(ii). Rather, as explained, these sections already alert providers to the very same risks covered by the omitted section 2.6 labeling and make clear that dose reduction may be a possible means of addressing them as determined by medical providers.

3. Novartis is also wrong to suggest (at 36–39) that there has been an agency change of position regarding FDA's safety and efficacy determination. As the district court recognized, FDA has maintained a consistent view from 2015 to the present day regarding the clinical value of the section 2.6 dosing regimen: that while a gradual-dosage approach was "'reasonable' for FDA to approve because it 'may' reduce the risks of adverse reactions [in certain patients], the agency has never taken the position that the study's conclusions were definitive or 'necessary' for the approval of Entresto." Dkt. 68 at 20 (quotations omitted).

Novartis's discussion of this Court's precedents is thus of no help, as those cases concern the sufficiency of an agency's explanation for treating two similarly situated items differently. *See* Br. 36–39 (first citing *Lilliputian Sys., Inc. v. Pipeline & Hazardous Materials Safety Admin.*, 741 F.3d 1309, 1313–14 (D.C. Cir. 2014); and then citing *Clean Wis. v. Environmental Prot.*

Agency, 964 F.3d 1145, 1162–63 (D.C. Cir. 2020) (per curiam)). That analogy fails for the reasons already discussed. FDA has maintained a consistent view regarding the clinical value of section 2.6; FDA has thoroughly explained its reasoning for approving the dosage carve-out; and any difference in treatment is readily explained by one of the purposes of the Hatch-Waxman scheme: to allow generic manufacturers to omit some patent-protected part of the reference drug labeling.

III. Entresto and the Generic Drug Contain the Same Active Ingredients.

The Hatch-Waxman Amendments also require that the generic drug have the same "active ingredients as" the brand-name drug. *Caraco*, 566 U.S. at 405; *see* 21 U.S.C. §§ 355(j)(2)(A)(ii), (4)(C); 21 C.F.R. § 314.92(a)(1). Active-ingredient sameness is based on the active ingredients' chemical identity. FDA regulations do not require that the two drugs have the same solid-state physical form. For example, if two active ingredients have the same chemical formulas but form different crystalline structures, they can be considered the same. 57 Fed. Reg. at 17958–59; FDA, *Guidance for Industry: ANDAs: Pharmaceutical Solid Polymorphism*, *supra*, at 5–6 (explaining that FDA rejected a proposal requiring active-ingredient

sameness to mandate the same "physical" characteristics and that as a result, a generic drug need not have the same physical form as the reference drug).

Under FDA regulations, active-ingredient sameness requires the generic drug to have the "same salt . . . of the same therapeutic moiety." 21 C.F.R. § 314.3(b). An "[a]ctive moiety" is the part of the molecule or ion that is "responsible for the physiological or pharmacological action of the drug substance." *Id.* A drug whose active ingredient contains a "different salt or ester of the active ingredient in the listed drug" is not identical. *Proposed Rule: Abbreviated New Drug Application Regulations*, 54 Fed. Reg. 28872, 28881 (July 10, 1989). A salt is a chemical compound consisting of negatively charged atoms (anions) and positively charged atoms (cations). FDA, *Regulatory Classification of Pharmaceutical Co-Crystals Guidance for Industry* 4 (Feb. 2018), https://perma.cc/GEE2-RTCR (Co-Crystals Guidance) (defining "salts"); Hawley's Condensed Chemical Dictionary 95, 275 (16th ed. 2016) (defining "anion" and "cation").

Different salts of the same active moiety are often distinguished based on the way in which the hydrogen atom in the chemical structure is replaced by a positively charged ion. *See* Hawley's Condensed Chemical

Dictionary, *supra*, at 1200 (explaining that a "salt" is the "compound formed when the hydrogen of an acid is replaced"). For example, if one active ingredient consists of the anion of the active moiety and a sodium cation, and another active ingredient consists of the anion of the active moiety and a hydroxyl cation (consisting of one hydrogen atom and one oxygen atom), the two active ingredients would be different salts of the same active moiety. As noted above, however, if two active ingredients have the same chemical formula but differ only in their physical structure, they are considered the same. Thus, if both active ingredients consist of the anion of the active moiety and a sodium cation, they are the same even if they are arranged in a different crystalline structure.

Entresto and the MSN generic have the same active ingredients. As described on the labeling of both drugs, the active ingredients are "anionic forms of sacubitril and valsartan, and sodium cations in the molar ratio of 1:1:3." Dkt. 13-1, at 3 (§ 11) (labeling for MSN generic); *see* Dkt. 1-1, at 11 (§ 11) (same for Entresto, which also lists water molecules). Faced with the plain language of the labeling, Novartis attempts to engineer a distinction by comparing the ingredients listed in Entresto's labeling not with MSN's labeling, but with one page from the "record show[ing] that MSN uses

sacubitril sodium and valsartan disodium in the manufacture of its products." Br. 54 (citing AR 1896). Novartis then argues that the two are not the same. *See* Br. 53–55. Unlike the generic drug, Novartis asserts, Entresto is "not composed of sacubitril sodium and valsartan disodium," but is instead a complex composed in relevant part of "anionic forms of sacubitril and valsartan" and "sodium cations." Br. 54.

But those are the same thing. By definition, "sacubitril sodium" means the salt formed by combining the anionic form of sacubitril with a sodium cation, and "valsartan disodium" means the salt formed by the anionic form of valsartan with two sodium cations (hence "disodium"). *See generally* Co-Crystals Guidance 4. And when they are combined together, the result is the anionic form of sacubitril, the anionic form of valsartan, and a total of three sodium cations—that is, "anionic forms of sacubitril and valsartan, and sodium cations in the molar ratio of 1:1:3." Novartis provides no response to this chemical analysis, which in any event is precisely the type of "scientific judgment within [FDA's] 'area of expertise'" to which this Court routinely defers. *Rempfer*, 583 F.3d at 867.

Novartis's efforts to identify a distinction instead amount to differences in nomenclature. Novartis argues that Entresto's labeling does

not mention sacubitril sodium or valsartan disodium, only anionic forms of sacubitril and valsartan. Br. 54. But the same is true of MSN's labeling. And in any event, because sacubitril sodium is composed of the anionic form of sacubitril and a sodium cation, the different wording does not reflect any chemical distinction. Nor, as Novartis contends, has FDA changed positions regarding whether Entresto's active ingredients are in a "sodium salt complex." Br. 54–55. The page on which Novartis relies (at AR 58 (emphasis added)) shows that FDA understood it was "scientifically valid" to describe Entresto's active ingredients as a "sodium salt complex," but that the agency was concerned that the term could cause confusion by suggesting that the "active ingredient is *a* salt," when it is a complex containing two salts and the active moiety is not a salt at all.

Similarly, Novartis's reliance on the use of the terms "sacubitril" and "valsartan" in the Orange Book is misplaced. Br. 56. Nothing about the Orange Book's listing of the active moieties rather than the active ingredients alters the undisputed fact that the active ingredients are not "sacubitril and valsartan" themselves, but rather the anionic form of those molecules along with sodium cations. As the district court explained, "by Novartis's own characterization, Entresto has always been labeled as

containing the *anionic* compounds" of sacubitril and valsartan, so the "nomenclature distinction" that Novartis identifies "does not reflect any difference in the chemical identity of the active drug ingredients." Dkt. 68, at 23.

CONCLUSION

For the foregoing reasons, the judgment of the district court should be affirmed.

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CERTIFICATE OF COMPLIANCE

This brief complies with the type-volume limit of Federal Rule of Appellate Procedure 32(a)(7)(B) because it contains 9,612 words. This brief also complies with the typeface and type-style requirements of Federal Rule of Appellate Procedure 32(a)(5)-(6) because it was prepared using Word for Microsoft 365 in Book Antiqua 14-point font, a proportionally spaced typeface.

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CERTIFICATE OF SERVICE

I hereby certify that on January 28, 2025, I electronically filed the foregoing brief with the Clerk of the Court for the United States Court of Appeals for the District of Columbia Circuit by using the appellate CM/ECF system.

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ADDENDUM

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21 U.S.C. § 355(j)(2)(A)

§ 355(j). Abbreviated new drug applications

(1) Any person may file with the Secretary an abbreviated application for the approval of a new drug.

(2)

(A) An abbreviated application for a new drug shall contain –

(i) information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a drug listed under paragraph (7) (hereinafter in this subsection referred to as a "listed drug");

(ii) (I) if the listed drug referred to in clause (i) has only one active ingredient, information to show that the active ingredient of the new drug is the same as that of the listed drug;

(II) if the listed drug referred to in clause (i) has more than one active ingredient, information to show that the active ingredients of the new drug are the same as those of the listed drug, or

(III) if the listed drug referred to in clause (i) has more than one active ingredient and if one of the active ingredients of the new drug is different and the application is filed pursuant to the approval of a petition filed under subparagraph (C), information to show that the other active ingredients of the new drug are the same as the active ingredients of the listed drug, information to show that the different active ingredient is an active ingredient of a listed drug or of a drug which does not meet the requirements of section 321(p) of this title, and such other information respecting the different active ingredient with respect to which the petition was filed as the Secretary may require;

. . .

(v) information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug referred to in clause (i) except for changes required because of differences approved under a petition filed under subparagraph (C) or because

the new drug and the listed drug are produced or distributed by different manufacturers;

. . .

(viii) if with respect to the listed drug referred to in clause (i) information was filed under subsection (b) or (c) for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, a statement that the method of use patent does not claim such a use.

. . .

21 C.F.R. § 314.3(b)

§ 314.3. Definitions.

(b) The following definitions of terms apply to this part and part 320 of this chapter:

. . .

Active moiety is the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.

. . .

Pharmaceutical equivalents are drug products in identical dosage forms and route(s) of administration that contain identical amounts of the identical active drug ingredient, *i.e.,* the same salt or ester of the same therapeutic moiety, or, in the case of modified-release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; do not necessarily contain the same inactive ingredients; and meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.

21 C.F.R. § 314.94(a)(8)(iv)

§ 314.94. Content and format of an ANDA.

ANDAs are required to be submitted in the form and contain the information required under this section. Three copies of the ANDA are required, an archival copy, a review copy, and a field copy. FDA will maintain guidance documents on the format and content of ANDAs to assist applicants in their preparation.

(a) ANDAs. Except as provided in paragraph (b) of this section, the applicant must submit a complete archival copy of the abbreviated new drug application that includes the following:

. . .

(8) Labeling –

. . .

(iv) ***Comparison of approved and proposed labeling.*** A side-by-side comparison of the applicant's proposed labeling including, if applicable, any Medication Guide required under part 208 of this chapter with the approved labeling for the reference listed drug with all differences annotated and explained. Labeling (including the container label, package insert, and, if applicable, Medication Guide) proposed for the drug product must be the same as the labeling approved for the reference listed drug, except for changes required because of differences approved under a petition filed under § 314.93 or because the drug product and the reference listed drug are produced or distributed by different manufacturers. Such differences between the applicant's proposed labeling and labeling approved for the reference listed drug may include differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(5)(F) of the Federal Food, Drug, and Cosmetic Act.

21 C.F.R. § 314.127(a)(7)

§ 314.127. Refusal to approve an ANDA.

(a) FDA will refuse to approve an ANDA for a new drug under section 505(j) of the Federal Food, Drug, and Cosmetic Act for any of the following reasons, unless the requirement has been waived under § 314.99:

. . .

(7) Information submitted in the ANDA is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for the listed drug referred to in the ANDA except for changes required because of differences approved in a petition under § 314.93 or because the drug product and the reference listed drug are produced or distributed by different manufacturers or because aspects of the listed drug's labeling are protected by patent, or by exclusivity, and such differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, nonprotected conditions of use.